REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Corrections on the record concerning the Information Disclosure Statement and amendments to the specification

Applicants wish to correct previous errors on the record.

On page 2 of the Information Disclosure Statement filed on December 30, 2009, Applicants provided a chart indicating that EP 1 265 659 was the corresponding patent to JP-A-2001-288080. EP 1 254 659 is the correct number of the corresponding patent to JP-A-20010288080. EP 1 254 659 was cited in the IDS filed on October 30, 2009, and has been considered by the Examiner. This error has no material impact on the prosecution of this application.

Page 13 of the Amendment and Reply filed November 30, 2009, states that:

> In the paragraph at lines 3-24 on page 46, each previous recitation of "(compound n)" is amended to "(compound n')." This amendment merely corrects an error in the English translation of the Japanese language specification and is supported by the specification from page 95, line 13 to page 97, line 5, which includes Tables 13 and 14.

It has been brought to the undersigned's attention that this typographical error was also originally present in the Japanese language PCT application. Applicants nevertheless respectfully assert that the typographical error is clear from the context of the specification and therefore the amendment is not new matter.

II. Status of the claims

Claims 1-4 and 6 are cancelled, and claims 6-20 are withdrawn. Claims 5 and 7-23 are pending, with claims 5 and 21-23 under examination. No claims are newly added, cancelled or amended.

III. Status of the rejections

Applicant acknowledges the withdrawal of previous rejections under the doctrine of obviousness-type double patenting, 35 U.S.C. §§ 101, 102(b), and 112, first and second paragraphs. Prior rejections under 35 U.S.C. § 103 have been maintained.

IV. Rejections under 35 U.S.C. § 103(a)

Claims 5, 21 and 23 are alleged to be rendered obvious by EP 1063228 ("Ichimori"). Action at pages 3-5. Claim 22 is rejected as obvious over the combination of Ichimori with U.S. Patent No. 5714469 to DeMarsh *et al.* ("DeMarsh"). Action at pages 5-7. Applicants respectfully traverse the rejection in view of previous remarks of record and for the additional reasons below.

A. Ichimori

Anticipation under 35 U.S.C. § 102 requires that the asserted prior art be enabling. Under 35 U.S.C. § 103, a conclusion of obviousness requires that the references relied upon be enabling in that it put the public in possession of the claimed invention. MPEP § 2145; *In re Hoeksema*, 399 F.2d 269, 274, 158 USPQ 596, 601 (CCPA 1968) "if the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public;" *see also Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 295, 297, 227 USPQ 657, 666, 667 (Fed. Cir. 1985). Thus, the enablement requirement under 35 U.S.C. § 103 parallels that under 35 U.S.C. §102, and is likely to be even more similar when the obviousness rejection is based a single reference, as here for claims 5, 21 and 23.

The requirement for enablement varies with the state of the art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Severe sepsis associated with organ failure, hypoperfusion and/or hypotension is a far more serious and complicated disease than sepsis. An expert committee distinguished the two conditions at, for example, pages 1646-1647, and Table 1 of Bone *et al.* "Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine," *Chest* 101: 1644-1655 (1992) (copy attached). The committee also note that "[w]hile recognizing that the disease process forms a continuum of severity, an analysis of several clinical trials has indicated that definable phases exist in that continuum which characterize populations at increased risk of morbidity and mortality." *Id.* at page 1647, first column.

The abstract of *British Medical Bulletin*, Vol. 55, pages 212-225 (1999) (available at http://bmb.oxfordjournals.org/cgi/reprint/55/1/212.pdf, accessed November 27, 2009) states that:

> [d]espite intensive efforts, the development of novel drugs for the treatment of sepsis has proved to be extremely difficult. A large number of clinical trials have ended in failure. A critical analysis of this record suggests that there is no single reason for these problems. Rather, the explanation lies in part with unexpected failures in the drugs themselves, and in part with the difficulties of trial design in this particular group of patients. In future, trials in this area are likely to be more highly focused, with even stricter protocol definitions to try and ensure a homogeneous patient population

This article demonstrates that the person of ordinary skill in the art recognizes that treatment of some aspects of sepsis has repeatedly failed to demonstrate treatment of severe sepsis, such as is associated with organ failure, hypoperfusion and/or hypotension.

Finally, as disclosed in the specification, clinical trials with antiinflammatory mediator therapy for severe sepsis patients had not shown even any *expected* effects. That is "[i]t has been also considered difficult for a drug that suppresses each one of complexly intertwined inflammatory mediators to show high effectiveness." Specification, page 7, lines 17-31.

Accordingly, the person of ordinary skill at the time of filing recognizes (a) that severe sepsis associated with organ failure, hypoperfusion and/or hypotension is a far more serious, complicated, and lethal disease than sepsis, (b) that the area is highly unpredictable and (c) that a large amount of experimentation is needed.

In this context, the person of ordinary skill must now consider the disclosure of Ichimori for the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. It is here that Ichimori is clearly most deficient.

Ichimori discloses compounds that are effective in inhibiting NO and cytokine production from RAW264.7 cells *in vitro* (page 81-84). When compounds 1 or 3 were administered to female BALB/c mice one hour *before* administration of LPS, compounds 1 and 3 inhibited NO production, and compound 1 inhibited cytokine production (pages 84-85).

First, Ichimori's administration of a compound one hour *before* challenge with LPS is not reasonably relevant to the *treatment* of disease, especially as the term would be used and understood in the clinical context. Treatment, in the context of sepsis or severe sepsis presupposes the existence of either disease. Thus, administration of a compound before challenge is not "treatment." In other words, how does administration of a drug before challenge with LPS relate to treatment of sepsis in a person in whom high levels of LPS have been present for periods of hours or days and, especially in severe sepsis, who has now developed a suite of immune complications, organ failure, and the like?

Second, and more importantly, the person of ordinary skill would not consider that administration of a compound one hour *before* challenge with LPS would be reasonably predictive of treatment in an individual who is already suffering from disease. This is especially true for a person presenting with severe sepsis associated with organ failure, hypoperfusion and/or hypotension, a more advanced and complicated disease with a high rate of mortality. *See e.g.* Bone *et al. Chest* 101: 1644-1655 (1992), *British Medical Bulletin* 55: 212-225 (1999).

Finally, Ichimori's 'treatment' of sepsis is not enabling of the present claims because "sepsis" is distinguished from "severe sepsis associated with organ failure, hypoperfusion and/or hypotension," in view of Bone *et al. Chest* 101: 1644-1655 (1992). Ichimori fails to show a therapeutic effect of the compound of the present invention against severe sepsis because it was not tested in animals with severe sepsis.

Thus, the "working examples" provided by Ichimori are wholly insufficient to enable the present invention. An undue quantity of experimentation is needed to make or use the invention based on the content of Ichimori, especially in view of the difficulties and failure of others described in the *British Medical Bulletin* article. Accordingly, Ichimori does not place the public in possession of the claimed invention and therefore is insufficient to render obvious the claims.

By comparison with Ichimori, Applicants have demonstrated a therapeutic effect afforded by the administration of the compounds after lapse of a considerable time after LPS administration, and induction of severe sepsis in test animals.

In response to Applicants' previous arguments, the Action (pages 4-5) does not address the issue of enablement, but asserts only that the person of ordinary skill "would be motivated to employ those compounds taught by Ichimori in the method of treating severe sepsis." Action at page 5. In view of the barriers to experimentation and the failures of others, the argument forwarded by the Office is little more than an invitation to experiment, or is "obvious to try," The courts have repeatedly held that "obvious to try" does not constitute obviousness when the only motivation relates to general research in an *unpredictable field*. For example, in *In re Kubin* 561 F.3d 1351 (Fed. Cir. 2009), the court identified that an impermissible "obvious to try" situation occurs where "what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Kubin* 561 F.3d at 1359 (citing *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)) ((emphasis added). Ichimori at most provides a motivation for experiment, but this is an insufficient basis under the law to render obvious the present claims.

Moreover, the Action does not directly address the assertion of "unmet and long-felt need," arguing only that Ichimori provides a motivation. Action at page 5. Providing a motivation is not equivalent to providing an unmet and long-felt need. Further, meeting a long-felt need is objective evidence of non-obviousness, and objective indicia of non-obviousness "is not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness" that must be given full consideration. *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365, 86 U.S.P.Q.2d 1196 (Fed. Cir. 2008). The Office's dismissal of Applicants' objective evidence of long-felt need as merely "unpersuasive," without providing reasoned argument and explanation, is neither the *full consideration* under *Ortho* 520 F.3d 1358, and is insufficient as a procedural matter in as much as Applicants have no basis to evaluate or address the rejection.

For the foregoing reasons, Ichimori does not render obvious claims 5, 21 and 23. Applicants respectfully request reconsideration and withdrawal of the rejection.

B. Ichimori with DeMarsh

DeMarsh is cited for its disclosure of administering ceftazidime for the treatment of sepsis. The argument at page 7 of the Action that the combination with Ichimori "flows logically from their having been taught individually in the prior art," which presumes that Ichimori teaches and enables the invention of claims 5, 21 and 23. The disclosure of DeMarsh does not, however, remedy the many defects of Ichimori in regard claim 22, or claims 5, 21 and 23. That is, the combination of Ichimori and DeMarsh does not disclose or enable the claimed method of treatment of severe sepsis associated with organ failure, hypoperfusion and/or hypotension, nor counter the invention's satisfaction of a long-felt unmet need in relation to *severe* sepsis.

C. Conclusion

For the above reasons, claims 5 and 21-23 are novel and unobvious. Applicants respectfully request reconsideration and withdrawal of the rejection.

V. Obviousness-type double patenting rejections

At pages 7-8 of the Action, claims 5 and 21-23 are rejected under the doctrine of obviousness type double patenting as obvious variants of claim 32 of U.S. Patent No. 6,495,604. Applicants respectfully traverse the rejection which relies on the same reasoning as the rejections under 35 U.S.C. § 103, and is respectfully believed to be overcome for the same reasons.

CONCLUSION

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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